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FULL PAPER

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Design, preparation, and characterization of Fe_3O_4 nanoparticles encapsulating β-cyclodextrin-bearing guanidine as a highly efficient and reusable heterogeneous base catalyst for synthesis of 3,4-dihydropyrano[3,2-*c*]chromenes

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Chromene substructure is an important structural motif present in a variety of medicines, natural products, and materials showing biological activities. Here, a simple and convenient procedure for the synthesis of 3,4-dihydropyrano [3,2-*c*]chromene derivatives is described. For this purpose, Fe_3O_4 nanoparticles supported on β-cyclodextrin-guanidine were successfully prepared and used as catalyst. The structure of this catalyst was assigned by Fourier transform infrared spectroscopy, X-ray diffraction, scanning electron microscopy, thermal gravimetric analysis, and vibrating sample magnetometer techniques. The prepared nanocomposites were used as a highly active, heterogeneous, and reusable nanocatalyst for the one-pot, three-component reaction of 4-hydroxycoumarin, aromatic aldehydes, and ethyl cyanoacetate. This method has advantages such as mild conditions, high yields, easy workup and simple purification of products, little catalyst loading, cost efficiency, and reusability of the catalyst.

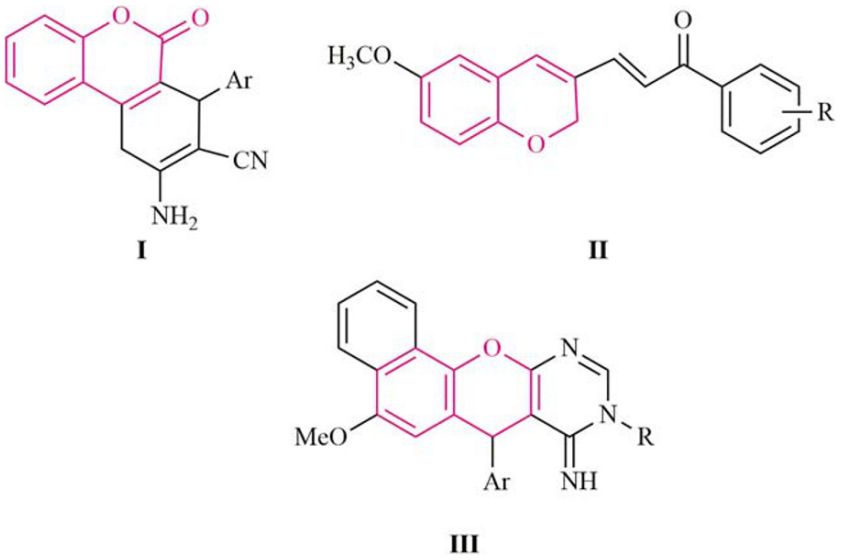
KEYWORDS

cyclodextrin, dihydropyrano[3,2-c]chromene, Fe_3O_4, heterogeneous catalyst, magnetic nanoparticles

1 | INTRODUCTION

Chromenes, common heterocyclic motifs containing an oxygen atom, exist extensively in nature and show several biological and therapeutic activities, including antiacetylcholinesterase,[1] antiproliferative,[2] antibacterial,[3] antioxidant,[4] and antitumor[5] properties. Chromenes and their derivatives isolated from plants are widely used to treat diverse ailments including hypertension, diabetes, cancer, arthritis, and diarrhea.[6] The chemical structures of some bioactive chromenes are shown in Scheme 1. Multicomponent synthesis of chromene and its derivatives has been developed using a variety of catalysts such as L-prolin/SiO_2, SO_3-SBA-15,[7] GO,[8] SBA-Py-Diph,[9] La-MOF, SBA-15@DABCO(1,-4-diazabicyclo[2.2.2]octane), silica-bonded 2-HEAA, and *p*-TSA.[10]

In addition, dihydropyrano[3,2-*c*]chromene and its derivatives show antimicrobial, antifungal,[11] and Acetylcholinesterase (AChE) inhibitory[12] activities. Therefore, the development of efficient methods for the synthesis of these important heterocycles has attracted researchers' attention. Various methods have been reported for the synthesis of these compounds in the presence of a variety of catalysts, such as thiourea dioxide,[13] DABCO,[14] DBU (1,8-Diazabicyclo[5.4.0]undec-7-ene),[15]



SCHEME 1 Some examples of bioactive chromenes

dehydroabietylamine–cinchonine–squaramide,[12] magnetic nanoparticles tag: piperidinium benzene-1,-3-disulfonate ionic liquid,[16] polypyrrole/Fe_3O_4/Carbon nanotube (CNT),[17] ammonium acetate,[18] Ni(II)-functionalized Li^+-montmorillonite,[19] sodium benzenesulfinates,[20] sodium malonate,[21] nano-SiO_2,[22] o-benzene disulfonimide,[23] potassium phthalimide,[24] crown ether complex cation ionic liquids,[25] and *N*,*N*-dimethylbenzylamine.[26]

Cyclodextrins (CDs) are cyclic oligomers made up of α-(1,4)-linked D-glucopyranose units. The practically important CDs are α-, β-, and γ-CD, which are composed of six, seven, and eight units, respectively. All CDs possess a truncated cone or torus structure. Due to the presence of hydroxyl groups, the exterior surface of each CD is hydrophilic, while the interior cavity is hydrophobic and nonpolar.[27] CDs have the ability to encapsulate a variety of guest molecules, such as aliphatic and aromatic hydrocarbons, acids, amines, alcohols, and small inorganic anions, through host–guest interactions.[28] In addition, the hydroxyl groups of CDs make them appropriate for modification and functionalization.[29] CDs have therefore been used as catalysts in various organic reactions.[30–33] Guanidine and its derivatives have been used in different organic reactions as a strong organobase catalyst.[34–36] Additionally, guanidines are found to be asymmetric catalysts in various reactions, including Henry, aza-Michael, phospha-Michael, Diels–Alder, protonation, electrophilic amination, and nucleophilic epoxidation reactions.[37] Separation and recycling of the catalyst are important factors that have been highly regarded in recent years.[38] Immobilization of homogeneous organic catalysts on various support materials is a sustainable method to recover and recycle catalysts. Owning to their unique structures and properties, magnetic nanoparticles can serve as a highly efficient catalyst supports. Magnetically supported catalysts are considered as green catalysts because they can be readily separated from the reaction media by a simple magnetic separation step without any additional purification.[39,40] There are various reports on applying Fe_3O_4 nanoparticle-supported *β*-cyclodextrin as catalyst in organic synthesis that indicate the efficiency of hybrid magnetic catalysts.[41–44]

Herein, considering the importance of chromenes and with the aim of developing an efficient, reusable, heterogeneous, cost-effective, and environmentally friendly catalyst for the synthesis of these compounds, amino-functionalized β-CD was prepared and grafted onto Fe_3O_4 nanoparticles via the chemical co-precipitation approach. The prepared catalyst's efficiency was explored in the synthesis of dihydropyrano [3,2-*c*]chromenes.

2 | EXPERIMENTAL

2.1 | General

All commercially available reagents were used without further purification and purchased from Merck, Fluka, and Aldrich in high purity. The solvents used were purified by standard procedure. Fourier transform infrared (FT-IR) spectra were obtained as KBr pellets on a Perkin Elmer 550 spectrometer in the range 400–4,000 cm^{-1} (Massachusetts, USA). ^1H NMR spectra were recorded in $CDCl_3$ solvent on a Bruker DRX-400 spectrometer (Bruker Daltonics, Bremen Germany) with tetramethylsilane as the internal reference. A BANDELIN ultrasonic HD 3200 with probe model KE

76 (Berlin, Germany) was used to produce ultrasonic irradiation and homogenize the reaction mixture. Field-emission scanning electron microscopy (FT-SEM) of the nanocatalyst was performed on an AIS2100 instrument (Seoul, Korea). Thermogravimetric analysis (TGA) was carried out with a STA1500 (Rheometric Scientific, Piscataway, NJ) instrument at a heating rate of 10°C/min under an inert nitrogen atmosphere. X-ray diffraction (XRD) patterns of nanostructures were taken using Cu Kα radiation ($\lambda = 1.5406$A) on a Holland Philips Xpert X-ray (Almelo, Holland) powder diffraction diffractometer. The magnetic properties of nanoparticles were measured by a vibrating sample magnetometer (VSM, PPMS-9 T, San Diego, CA, USA) at 300 K at the University of Kashan, Kashan, Iran. Determination of the trace metal ions was carried out using a simultaneous Inductively coupled plasma-optical emission spectrometry (ICP-OES) (Varian Vista-Pro, Springvale, Australia) coupled to a V-groove nebulizer and equipped with a charge coupled device (CCD). The elemental analyses (C, H, N) were obtained from a Carlo ERBA Model EA 1108 analyzer (Milan, Italy). Melting points were obtained using a Yanagimoto micro melting point apparatus (Kyoto, Japan) and are uncorrected. The purity determination of the substrates and reaction monitoring were accomplished by thin-layer chromatography (TLC) on silica-gel polygram SILG/UV 254 plates (Merck Company).

2.2 | Preparation of *β*-cyclodextrin-guanidine

β-cyclodextrin-guanidine (β-CD-GA) was prepared according to the previously reported procedure.[45,46] First, a solution of β-CD (1 g) and NaOH (30 ml, 22% m/v) was vigorously stirred at room temperature for 24 hr to deprotonate the hydroxyl groups of β-CD. Then, 0.4 g of guanidine powder (GN) was dissolved in 5 ml of deionized water. The guanidine (GA) solution was added dropwise to the β-CD solution and the mixture was stirred for 2 hr. Next, 0.07 ml of epichlorohydrin (EPH) was added and the reaction mixture was stirred for another 3 hr. The mixture was concentrated to about 15 ml and cold ethanol was added until a gummy precipitate appeared. The precipitate was washed with ethanol and acetone and dried in an oven at 50°C.

2.3 | Preparation of Fe_3O_4 nanoparticle-supported β-CD-GA

Fe_3O_4-β-CD-GA was prepared by a one-step co-precipitation method according to a previously reported procedure.[46] Briefly, $FeCl_3.6H_2O$ (1.10 g), $FeCl_2.4H_2O$ (0.43 g) and β-CD-GA (0.7 g) were dissolved in distilled water (30 ml) and the mixture was heated to 90°C with vigorous stirring. Then, concentrated ammonia (25%) was added dropwise to the reaction mixture under an N_2 atmosphere. Stirring was continued for 60 min at 90°C. The resulting nanoparticles were separated from the solution using an external magnetic field, washed several times with deionized water, and dried in a vacuum oven. Bare Fe_3O_4 Magnetic nanoparticles (MNPs) were prepared using this method without the addition of β-CD.

2.4 | General procedure for the synthesis of dihydropyrano[3,2-*c*]chromene derivatives catalyzed by Fe_3O_4-β-CD-GA

A mixture of aromatic aldehyde (1 mmol), 4-hydroxycoumarin (1 mmol, 0.16 g), and ethyl cyanoacetate (1.1 mmol, 0.11 ml) in the presence of Fe_3O_4-β-CD-GA nanoparticles (0.05 g) in 5 ml of ethanol was refluxed for the appropriate time as indicated in Table 4. The progress of the reaction was monitored by TLC. At the end of the reaction and after cooling to room temperature the catalyst was separated with an external magnet. Then, distilled water (5 ml) was added to the mixture and the solid product was filtered off and washed with water and cold diethyl ether to give the pure product. All of the products were identified by physical and spectroscopic data (For IR and ^{1}H NMR spectra, see Supporting Information)."

2-Amino-4-(4-nitrophenyl) 3-carboethoxy-4*H*,5*H*-pyrano[3,2-*c*]chromene-5-one (**4a**): Yellow solid, m.p. = 235–236°C (m.p. = 232–233°C[47]). IR (KBr)/ν (cm^{-1}): 3440, 3,326, 1,719, 1,688, 1,661, 1,611, 1,512, 1,376, 1,284. ^{1}H NMR ($CDCl_3$, 400 MHz)/δ (ppm): 1.15 (3H, t, J = 7.2, CH_3), 4.04–4.10 (2H, m, CH_2), 5.03 (1H, s, CH), 6.54 (2H, broad s, NH_2), 7.34 (1H, d, J = 7.6 Hz), 7.39 (1H, d, J = 7.6 Hz), 7.54 (2H, d, J = 8.8 Hz), 7.58–7.62 (1H, m), 7.86 (1H, dd, J = 8, 1.2 Hz), 8.12 (2H, d, J = 8.8 Hz).

2-Amino-4-(3-nitrophenyl) 3-carboethoxy-4*H*,5*H*-pyrano[3,2-*c*]chromene-5-one (**4b**): Yellow solid, m.p. = 235–236°C (m.p. = 228–230°C[48]). IR (KBr)/ν (cm^{-1}): 3432, 3,313, 1,710, 1,687, 1,657, 1,610, 1,535, 1,374, 1,277. ^{1}H NMR ($CDCl_3$, 400 MHz)/δ (ppm): 1.16 (3H, t, J = 7.2, CH_3), 4.06–4.10 (2H, m, CH_2), 5.03 (1H, s, CH), 6.49–6.62 (2H, broad s, NH_2), 7.33–7.44 (3H, m), 7.60 (1H, t, J = 7.6 Hz), 7.77 (1H, d, J = 7.6 Hz), 7.87 (1H, d, J = 8 Hz), 8.04 (1H, d, J = 7.6 Hz), 8.17 (1H, s). Anal. calcd for $C_{21}H_{16}N_2O_7$: C 61.77, H 3.95, N, 6.86%; found: C 61.90, H 3.95, N 6.88%.

2-Amino-4-(4-chlorophenyl) 3-carboethoxy-4*H*,5*H*-pyrano[3,2-*c*]chromene-5-one (**4c**): White solid, m.p. = 189–191°C

(m.p. = 188–190°C[47]). IR (KBr)/ν (cm^{-1}): 3466, 3,313, 1,717, 1,688, 1,660, 1,613, 1,528, 1,489, 1,373, 1,285, 1,196. ^{1}H NMR ($CDCl_3$, 400 MHz)/δ (ppm): 1.78 (3H, t, J = 7.2, CH_3), 4.03–4.12 (2H, m, CH_2), 4.90 (1H, s, CH), 6.42–6.58 (2H, broad s, NH_2), 7.21 (2H, d, J = 8.4 Hz), 7.29–7.36 (4H, m), 7.55–7.59 (1H, m), 7.83 (1H, dd, J = 8, 1.6 Hz).

2-Amino-4-(2-chlorophenyl) 3-carboethoxy-4*H*,5*H*-pyrano[3,2-*c*]chromene-5-one (**4d**): White solid, m.p. = 218–220°C (m.p. = 221–223°C[48]). IR (KBr)/ν (cm^{-1}): 3397, 3,282, 1,716, 1,689, 1,648, 1,610, 1,527, 1,373, 1,283, 1,198. ^{1}H NMR ($CDCl_3$, 400 MHz)/δ (ppm): 1.16 (3H, t, J = 7.2, CH_3), 4.03–4.11 (2H, m, CH_2), 5.25 (1H, s, CH), 6.52 (2H, broad s, NH_2), 7.08–7.18 (2H, m), 7.25 (1H, s), 7.30–7.35 (2H, m), 7.39 (1H, d, J = 6.8 Hz), 7.53–7.58 (1H, m), 7.84 (1H, d, J = 8.0 Hz).

2-Amino-4-(3-chlorophenyl) 3-carboethoxy-4*H*,5*H*-pyrano[3,2-*c*]chromene-5-one (**4e**): White solid, m.p. = 214–216°C. IR (KBr)/ν (cm^{-1}): 3406, 3,306, 1,728, 1,688, 1,655, 1,611, 1,527, 1,372, 1,287, 1,196. ^{1}H NMR ($CDCl_3$, 400 MHz)/δ (ppm): 1.19 (3H, t, J = 7.2 Hz, CH_3), 4.05–4.10 (2H, m, Hz, CH_2), 5.00 (1H, s, CH), 6.45 (2H, broad s, NH_2), 6.90–6.94 (1H, m), 7.02–7.05 (1H, J = 7.6 Hz), 7.31–7.41 (3H, m), 7.54–7.58 (1H, m), 7.85 (1H, d, J = 8 Hz). ^{13}C NMR ($CHCl_3$, 100 MHz)/δ ppm: 14.19, 35.45, 60.16, 79.68, 107.21, 113.36, 116.95, 122.31, 124.41, 126.98, 127.00, 128.58, 129.24, 132.42, 133.85, 146.34, 152.67, 153.39, 157.93, 160.65, 168.53. Anal. calcd for $C_{21}H_{16}NO_5Cl$: C 63.40, H 4.05, N 3.52%; found: C 63.70, H 4.05, N 3.73%.

2-Amino-4-(2,4-dichlorophenyl) 3-carboethoxy-4*H*,5*H*-pyrano[3,2-*c*]chromene-5-one (**4f**): White solid, m.p. = 198–199°C (m.p. = 200–201°C[49]). IR (KBr)/ν (cm^{-1}): 3411, 3,291, 1,721, 1,691, 1,654, 1,611, 1,523, 1,374, 1,280, 1,198. ^{1}H NMR ($CDCl_3$, 400 MHz)/δ (ppm): 1.18 (3H, J = 7.2 Hz, CH_3), 4.03–4.14 (2H, m, CH_2), 5.20 (1H, s, CH), 6.53 (2H, broad s, NH_2), 7.15 (1H, dd, J = 8.4, 2 Hz), 7.28 (1H, d, J = 2 Hz), 7.32–7.37 (3H, m), 7.56–7.60 (1H, m), 7.84 (1H, d, J = 6.8 Hz).

2-Amino-4-(4-fluorophenyl)-3-carboethoxy-4*H*,5*H*-pyrano[3,2-*c*]chromene-5-one (**4g**): White solid, m.p. = 223–224°C (m.p. = 223–225°C[49]). IR (KBr)/ν (cm^{-1}): 3483, 3,315, 1,717, 1,687, 1,662, 1,610, 1,529, 1,510, 1,374, 1,288, 1,200. ^{1}H NMR ($CDCl_3$, 400 MHz)/δ (ppm): 1.17 (3H, t, J = 7.2, CH_3), 4.04–4.12 (2H, m, CH_2), 4.91 (1H, s, CH), 6.44 (2H, broad s, NH_2), 6.92 (2H, t, J = 8.8 Hz), 7.31–7.37 (4H, m), 7.55–7.59 (1H, m), 7.84 (1H, dd, J = 7.6, 1.6 Hz).

2-Amino-4-(2-fluorophenyl)-3-carboethoxy-4*H*,5*H*-pyrano[3,2-*c*]chromene-5-one (**4h**): White solid, m.p. = 223–224°C. IR (KBr)/ν (cm^{-1}): 3393, 3,271, 1,718, 1,690, 1,651, 1,610, 1,522, 1,372, 1,284, 1,198. ^{1}H NMR ($CDCl_3$, 400 MHz)/δ (ppm): 1.19 (3H, t, J = 7.2, CH_3), 4.06 (2H, q, J = 7.2, CH_2), 5.06 (1H, s, CH), 6.46–6.51 (2H, broad s, NH_2), 6.90–6.94 (1H, m), 7.03 (1H, t, J = 7.4 Hz), 7.12–7.17 (1H, m), 7.31–7.41 (3H, m), 7.56 (1H, t, J = 8.0 Hz), 7.85 (1H, d, J = 8.0 Hz). ^{13}C NMR ($CHCl_3$, 100 MHz)/δ ppm: 14.11, 31.35, 60.05, 78.59, 105.85, 113.41, 115.69, 116.92, 122.32, 123.57, 124.31, 128.58, 130.42, 131.84, 132.27, 152.72, 153.74, 158.10, 160.25, 160.64, 162.71, 168.78.

2-Amino-4-(2-bromophenyl)-3-carboethoxy-4*H*,5*H*-pyrano[3,2-*c*]chromene-5-one (**4i**): White solid, m.p. = 225–227°C. IR (KBr)/ν (cm^{-1}): 3397, 3,283, 1,717, 1,688, 1,649, 1,610, 1,527, 1,372, 1,283, 1,197. ^{1}H NMR ($CDCl_3$, 400 MHz)/δ (ppm): 1.16 (3H, t, J = 7.2, CH_3), 4.05–4.12 (2H, m, CH_2), 5.27 (1H, s, CH), 6.50–6.52 (2H, broad s, NH_2), 6.99–7.04 (1H, m), 7.18–7.22 (1H, m), 7.31–7.38 (3H, m), 7.47 (1H, dd, J = 1.2, 8.0 Hz), 7.55–7.59 (1H, m), 7.85 (1H, dd, J = 1.2, 8.0 Hz). ^{13}C NMR ($CHCl_3$, 100 MHz)/δ ppm: 14.34, 36.45, 60.06, 79.11, 106.02, 113.23, 116.92, 122.33, 124.00, 124.26, 126.93, 128.20, 132.32, 132.85, 133.34, 142.07, 152.73, 153.51, 157.99, 160.32, 168.85. Anal. calcd for $C_{21}H_{16}NO_5Br$: C 57.03, H 3.65, N 3.17%; found: C 57.11, H 3.52, N 3.18%.

2-Amino-4-(4-bromophenyl)-3-carboethoxy-4*H*,5*H*-pyrano[3,2-*c*]chromene-5-one (**4j**): White solid, m.p. = 190–192°C (m.p. = 193–194°C[49]). IR (KBr)/ν (cm^{-1}): 3419, 3,295, 1,717, 1,690, 1,651, 1,610, 1,520, 1,374, 1,279, 1,197. ^{1}H NMR ($CDCl_3$, 400 MHz)/δ (ppm): 1.17 (3H, t, J = 7.2, CH_3), 4.03–4.12 (2H, m, CH_2), 4.88 (1H, s, CH), 6.46–6.49 (2H, broad s, NH_2), 7.24 (1H, d, J = 8.4 Hz), 7.32–7.37 (3H, m), 7.54–7.58 (1H, m), 7.83 (1H, d, J = 8.0 Hz).

2-Amino-4-(3-methoxyphenyl)-3-carboethoxy-4*H*,5*H*-pyrano[3,2-*c*]chromene-5-one (**4k**): White solid, m.p. = 210–212°C. IR (KBr)/ν (cm^{-1}): 3412, 3,305, 1,695, 1,658, 1,634, 1,605, 1,539, 1,377, 1,272, 1,194. ^{1}H NMR ($CDCl_3$, 400 MHz)/δ (ppm): 1.18 (3H, t, J = 7.2 Hz, CH_3), 3.76 (3H, s, OMe), 4.07 (2H, q, J = 7.2 Hz, CH_2), 4.90 (1H, s, CH), 6.42–6.51 (2H, broad s, NH_2), 6.70 (1H, d, J = 5.4 Hz), 6.92–6.97 (2H, m),7.12–7.17 (1H, m),7.24–7.33 (2H, m), 7.52–7.56 (1H, m), 7.79–7.81 (1H, d, J = 7.2 Hz). ^{13}C NMR ($CHCl_3$, 100 MHz)/δ ppm: 14.27, 35.44, 55.20, 60.05, 80.11, 107.90, 111.72, 113.53, 114.69, 116.84, 121.01, 122.20, 124.28, 132.17, 145.97, 152.57, 153.24, 158.04, 159.36, 160.80, 168.74. Anal. calcd for $C_{22}H_{19}NO_6$: C 67.17, H 4.87, N 3.56%; found: C 67.42, H 4.87, N 3.53%.

2-Amino-4-(4-methoxyphenyl)-3-carboethoxy-4*H*,5*H*-pyrano[3,2-*c*]chromene-5-one (**4l**): White solid, m.p. = 165–167°C (m.p. = 160–162°C[49]). IR (KBr)/ν (cm^{-1}): 3399, 3,297, 1,695, 1,654, 1,608, 1,534, 1,510,

1,376, 1,282, 1,192. ^{1}H NMR ($CDCl_3$, 400 MHz)/δ (ppm): 1.19 (3H, t, J = 7.2, CH_3), 3.75 (3H, s, OMe), 4.07–4.10 (2H, m, CH_2), 4.88 (1H, s, CH), 6.41 (2H, broad s, NH_2), 6.78 (2H, d, J = 8.4 Hz), 7.29–7.35 (4H, m), 7.53–7.57 (1H, m), 7.82 (1H, d, J = 8.0 Hz).

2-Amino-4-(2-methylphenyl) 3-carboethoxy-4*H*,5*H*-pyrano[3,2-*c*]chromene-5-one (**4m**): White solid, m.p. = 221–224°C. IR (KBr)/ν (cm^{-1}): 3400, 3,290,1,686, 1,653, 1,609, 1,533, 1,376, 1,282, 1,195. ^{1}H NMR ($CDCl_3$, 400 MHz)/δ (ppm): 1.20 (3H, t, J = 7.2, CH_3), 2.29 (3H, s, CH_3), 4.04–4.13 (2H, m, CH_2), 4.90 (1H, s, CH), 6.43 (2H, broad s, NH_2), 6.97 (1H, d, J = 6.8 Hz), 7.11–7.16 (3H, m), 7.31–7.36 (2H, m), 7.53–7.58 (1H, m), 7.84 (1H, dd, J = 8, 1.2 Hz). ^{13}C NMR ($CHCl_3$, 100 MHz)/δ ppm: 14.21, 21.50, 35.43, 60.03, 80.37, 108.07, 113.59, 116.85, 122.24, 124.27, 125.62, 127.57, 127.93, 129.20, 132.13, 137.55, 144.19, 152.60, 153.21, 157.96, 160.81, 168.80. Anal. calcd for $C_{22}H_{16}NO_5$: C 70.02, H 5.07, N 3.71%; found: C 70.31, H 5.29, N 3.90%.

2-Amino-4-phenyl-3-carboethoxy-4*H*,5*H*-pyrano [3,2-*c*]chromene-5-one (**4n**): White solid; m.p. = 208–209°C (m.p. = 209–211°C[47]). IR (KBr)/ν (cm^{-1}): 3413, 3,307, 1,688, 1,655, 1,609, 1,543, 1,492, 1,377, 1,278, 1,192, 1,053. ^{1}H NMR ($CDCl_3$, 400 MHz)/δ (ppm): 1.12 (3H, t, J = 7.2, CH_3), 4.10 (2H, q, J = 6.8 Hz CH_2), 4.90 (1H, s, CH), 6.18–6.53 (2H, broad s, NH_2), 7.16 (1H, d, J = 6.8 Hz), 7.22–7.25 (3H, m), 7.30–7.37 (3H, m), 7.55 (1H, t, J = 8.0 Hz), 7.83 (1H, d, J = 8.0 Hz). Anal. calcd for $C_{21}H_{17}NO_5$: C 64.41, H 4.72, N 3.55%; found: C 64.70, H 4.99, N 3.58%.

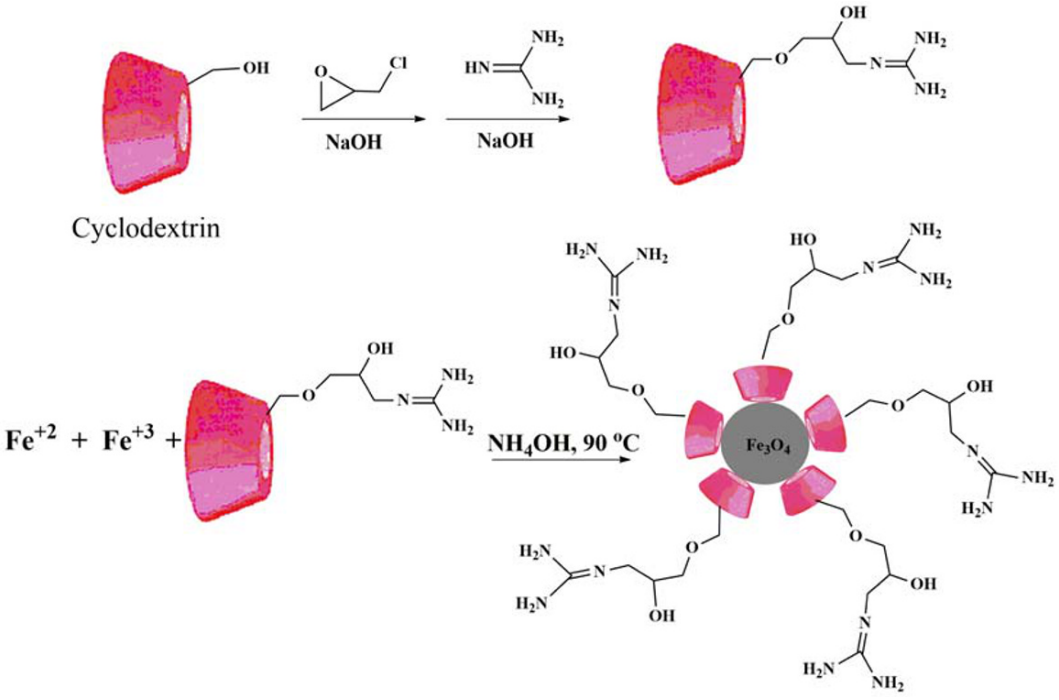
3 | RESULTS AND DISCUSSION

3.1 | Preparation and characterization of catalyst

The synthetic strategy for the preparation of magnetic nanoparticle-supported β-CD-GA is shown in Scheme 2.

In the beginning, deprotonation of hydroxyl groups on CDs was performed in an alkaline aqueous solution at room temperature. Then, GN was added to the obtained solution to activate GA. After adding EPH to the solution, substitution of chlorine and ring-opening of epoxide occurred. A simple co-precipitation method was applied for the preparation of Fe_3O_4-supported β-CD-GA. The catalyst was obtained from $FeCl_2$ and $FeCl_3$ as iron precursors, and β-CD-GA that mixed together in the reaction medium. After successful preparation of Fe_3O_4-β-CD-GA, the catalyst was characterized by FT-IR, SEM, XRD, TGA, and VSM techniques.

The FT-IR spectra of the β-CD-GA and Fe_3O_4-β-CD-GA are shown in Figure 1. The spectrum of β-CD-GA (Figure 1a) shows an absorption band at 3463 cm^{-1} that is related to the overlap between water molecules, the primary and secondary O–H groups of β-CD, and the N–H stretching of guanidine. The absorption peaks at 1661 and 1,440 cm^{-1} are related to C=N and C–N of guanidine, respectively. Characteristic peaks of β-CD at 1156 and 1,034 (attributed to the C–O of the secondary alcohol and C–O–C, respectively) are present with a small shift compared to the same



SCHEME 2 Schematic presentation of β-CD-GA grafting onto Fe_3O_4 nanoparticles

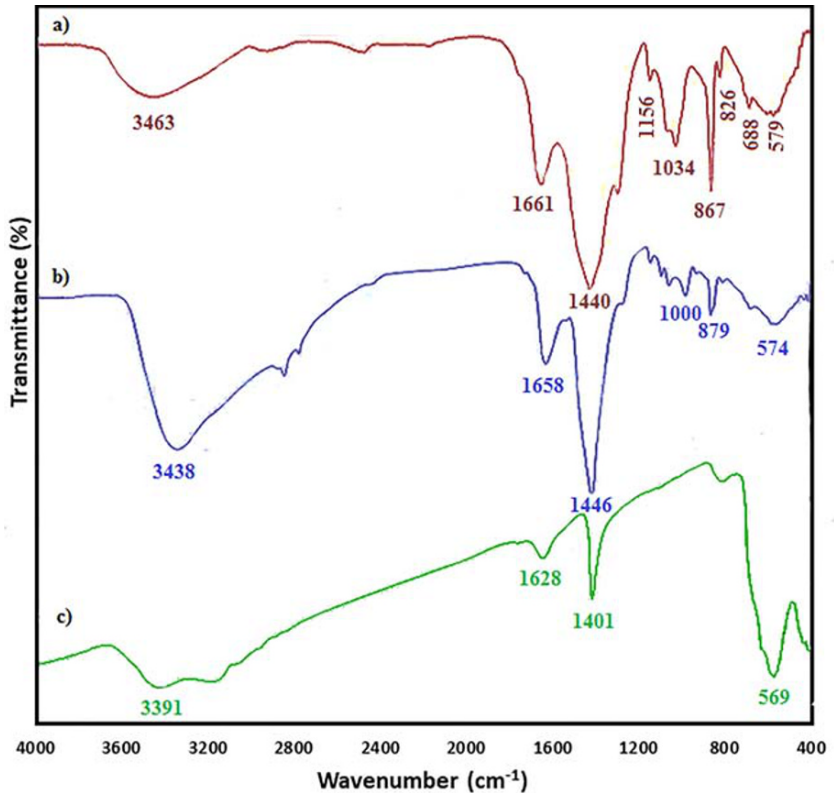


FIGURE 1 IR spectra of (a) β-CD-GA, (b) Fe_3O_4-β-CD-GA, and (c) Fe_3O_4

peaks in pure CD.[45] The peak at 569 in the spectrum of Fe_3O_4 (Figure 1c) is related to the Fe–O bond, which is shifted to 574 cm^{-1} after being supported with β-CD-GA (Figure 1b).

The XRD patterns of Fe_3O_4 nanoparticles and Fe_3O_4-β-CD-GA are illustrated in Figure 2. All of the peaks are in good agreement with the standard XRD pattern of Fe_3O_4 (JCPDS card No. 75–0449) in terms of position and relative intensity. No obvious difference between the two XRD patterns reveals that the grafting of β-CD-GA onto Fe_3O_4 nanoparticles did not result in a phase change of Fe_3O_4 nanoparticles. The average crystallite size of Fe_3O_4-β-CD-GA by applying the Scherrer formula was calculated 32 nm.

To find the morphological characteristics of the nanoparticles SEM was carried out (Figure 3). The SEM image of Fe_3O_4-β-CD-GA shows semi spherical particles with average size of about 49 nm.

The magnetic properties of the prepared Fe_3O_4 nanoparticles and final catalyst were characterized by VSM (Figure 4). Comparison of the room temperature magnetization curves of Fe_3O_4 nanoparticles and Fe_3O_4-β-CD-GA indicates that the saturation magnetization of Fe_3O_4-β-CD-GA because of the nonmagnetic properties β-CD-GA is less than that of the bare Fe_3O_4 nanoparticles. The saturation magnetization values were found to be 52.29 and 29.53 emu/g for nano Fe_3O_4 and Fe_3O_4-β-CD-GA, respectively.

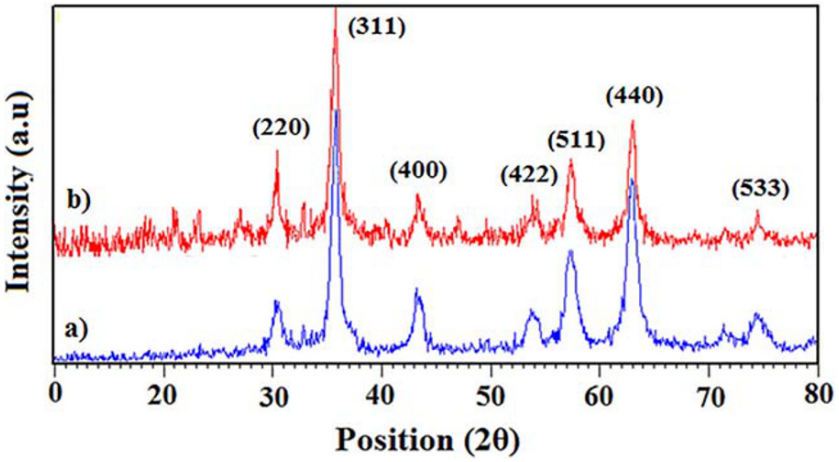


FIGURE 2 XRD patterns of (a) nano-Fe_3O_4 and (b) Fe_3O_4-β-CD-GA

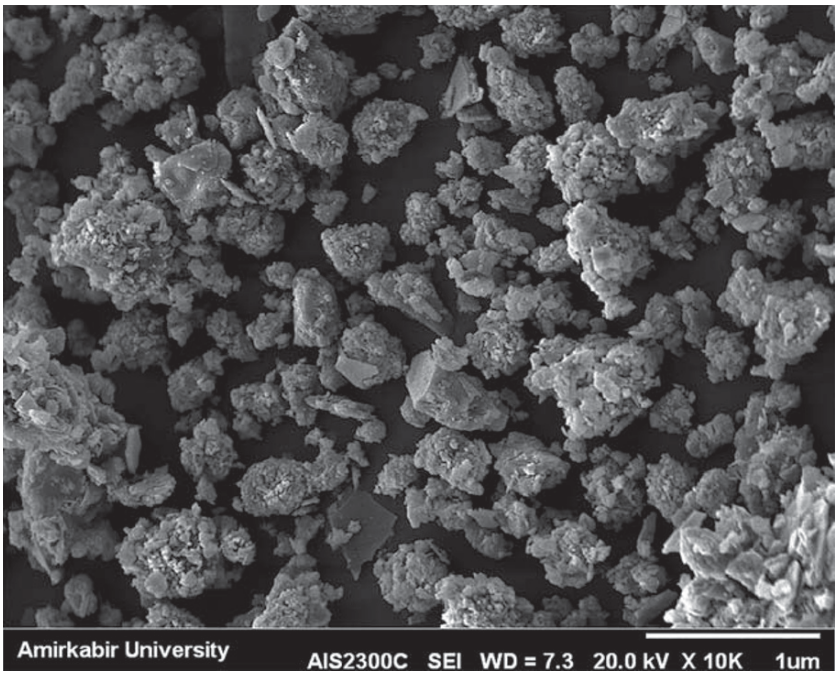


FIGURE 3 SEM image of Fe_3O_4-β-CD-GA

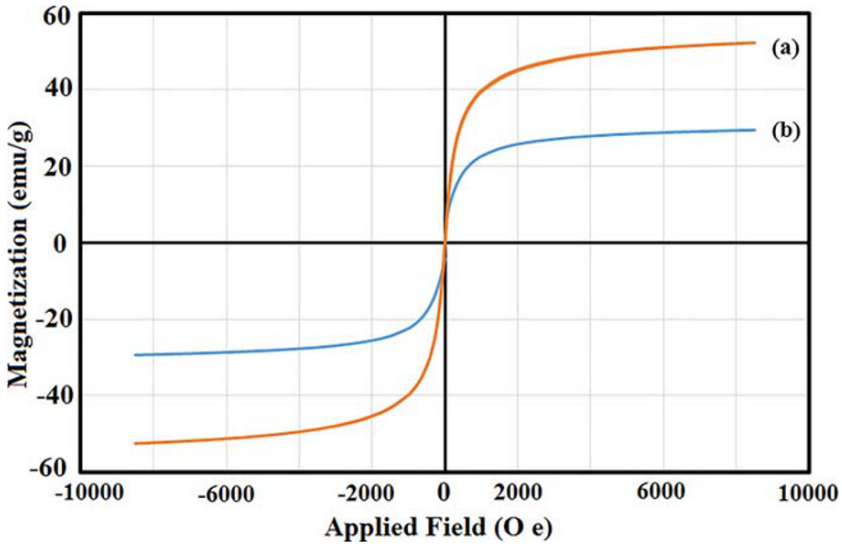


FIGURE 4 VSM curve of analysis of (a) Fe_3O_4 nanoparticles and (b) Fe_3O_4-β-CD-GA

The thermal stability and composition of Fe_3O_4-β-CD-GA were analyzed by TGA (Figure 5). The weight loss at temperatures below 200°C is most likely due to the elimination of the adsorbed water or trapped solvent. The other degradation stage between about 220 and 600°C with a weight loss of approximately 12% can be attributed to the decomposition of organic groups.

3.2 | Catalytic activity of the prepared catalyst in the synthesis of dihydropyrano [3,2-*c*]chromene derivatives

In this study, the reaction of aromatic aldehydes, 4-hydroxycoumarin, and ethyl cyanoacetate in the presence of Fe_3O_4-β-CD-GA nanoparticles as a highly efficient catalyst was examined (Scheme 3).

Initially, in an attempt to develop an optimal catalytic system for the synthesis of dihydropyrano [3,2-*c*]chromene derivatives the reaction of 2-chlorobenzaldehyde (1 mmol), 4-hydroxycoumarin (1 mmol), and ethyl cyanoacetate (1.1 mmol) was selected as a model reaction. The reaction was carried out in the presence of different quantities of Fe_3O_4-β-CD-GA in ethanol as a solvent. The results are summarized in Table 1. The results of the controlled blank reaction showed that in the absence of a catalyst, no product was obtained even after 4 hr (Table 1, entry 1). It was found that the best results in terms of time and product yield were obtained in the presence of 0.05 g of

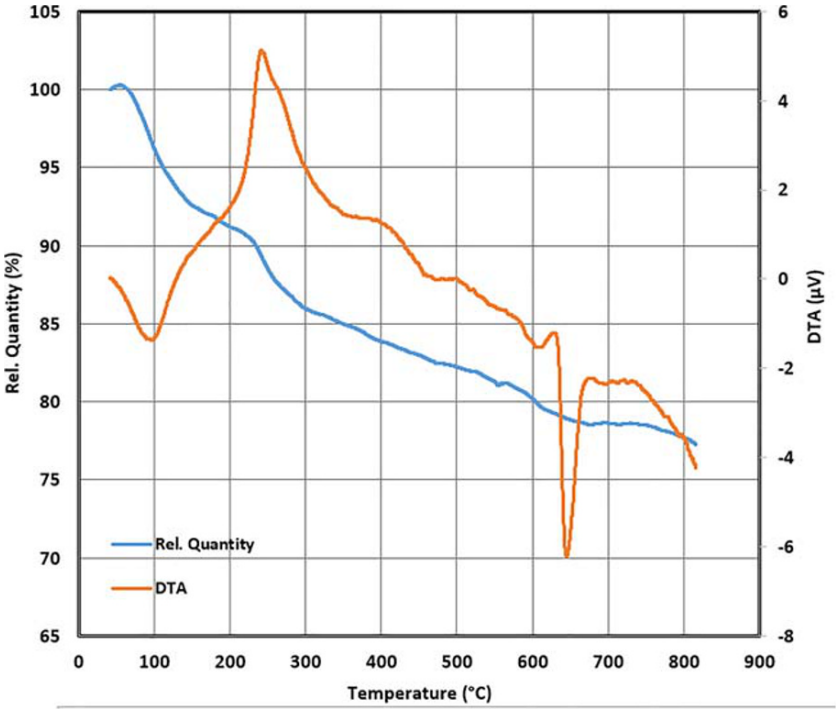
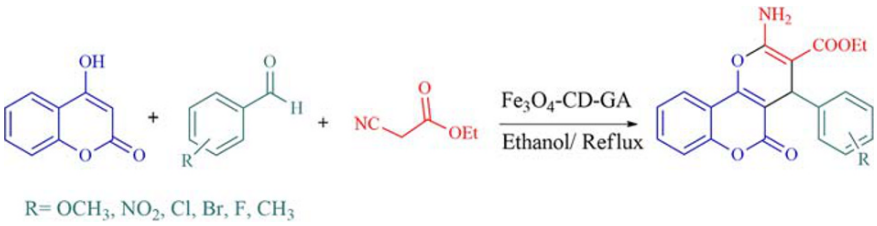


FIGURE 5 TGA curve of Fe_3O_4-β-CD-GA

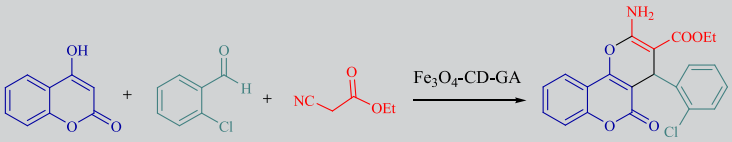


SCHEME 3 Synthesis of dihydropyrano[3,2-*c*]chromene derivatives

the catalyst (Table 1, entry 4), which was not improved by increasing the catalyst amount to 0.07 g (Table 1, entry 5).

To examine the role of Fe_3O_4, β-CD, and guanidine skeletons of the catalyst in the reaction, the condensation of 2-chlorobenzaldehyde, 4-hydroxycoumarin, and ethyl cyanoacetate in 5 ml of EtOH was performed in the presence of bare Fe_3O_4 nanoparticles, bare β-CD, and guanidine separately, and their catalytic activities were compared with that of Fe_3O_4-β-CD-GA (Table 2). The reaction using these skeletons as catalyst afforded the products in lower yields and longer reaction times

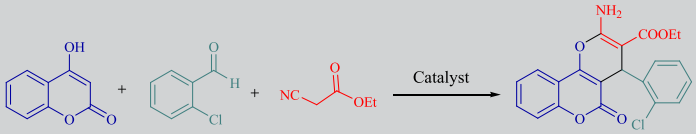
TABLE 1 Optimization of the catalyst amount for the synthesis of dihydropyrano[3,2-*c*]chromenes[a]



Entry	Catalyst amount (g)	Time (min)	Yield (%)[b]
1	No catalyst	240	0
2	0.02	80	69
3	0.03	80	80
4	0.05	80	89
5	0.07	80	89

[a]General reaction conditions: mixture of 2-chlorobenzaldehyde (1 mmol), 4-hydroxycoumarin (1 mmol), and ethyl cyanoacetate (1.1 mmol) in 5 ml of EtOH was refluxed.
[b]Isolated yields.

TABLE 2 Study of the role of Fe_3O_4 nanoparticles, β-CD, and guanidine skeletons of the catalyst on the synthesis of dihydropyrano[3,2-*c*]chromenes[a]



Entry	Catalyst/catalyst amount	Time (min)	Yield (%)[b]
1	Fe_3O_4-β-CD-GA (0.05 g)	80	89
2	Nano Fe_3O_4 (0.04 g)	180	30
3	β-CD (0.19 g)	180	42
4	Guanidine (0.01 g)	180	58

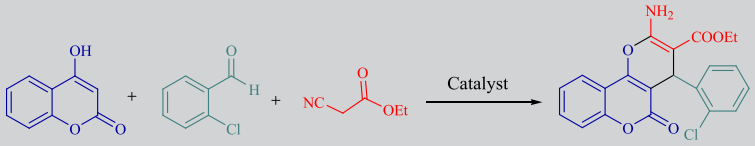
[a]General reaction conditions: mixture of 2-chlorobenzaldehyde (1 mmol), 4-hydroxycoumarin (1 mmol), and ethyl cyanoacetate (1.1 mmol) in 5 ml of EtOH was refluxed.
[b]Isolated yields.

compared with our method (Table 2, entries 2–4). These results can be attributed to the synergistic effects of β-CD, GA, and Fe_3O_4 nanoparticles, which increase the efficacy of the catalyst. The β-CDs are well known as host molecules with notable inclusion capabilities for a variety of small organic guests. In the prepared Fe_3O_4-β-CD-GA, the catalytic property of CD is due to the inclusion complex formation between reactants (aldehyde and ethyl cyanoacetate) and β-CD via hydrogen bonding between the carbonyl oxygen of the reactants and the outwardly hydroxyl groups of β-CD, which activates the reactants. Also, the formation of this complex can enhance the local amount of the substrates. In addition, functionalization of CD with GA brings the active catalytic center closer to substrates, leading to an increase in the reaction rate. Moreover, magnetic nanoparticles are appropriate supports for catalysts because they efficiently disperse active catalytic sites in the reaction medium.

To survey the effects of temperature and solvent, the reaction was performed in the presence of optimum amounts of Fe_3O_4-β-CD-GA in CH_2Cl_2, CH_3CN, H_2O, and EtOH solvents at room temperature and under reflux conditions (Table 3). The best results were obtained in EtOH under reflux conditions (Table 3, entry 6). Therefore, 0.05 g of the catalyst, EtOH as solvent, and reflux conditions were chosen as optimum terms.

In another study, to extend the scope of the reaction, the reaction of 4-hydroxycoumarine and ethyl cyanoacetate with a range of aromatic aldehydes was performed according to the general experimental procedure (Table 4). As shown in Table 4, various aromatic aldehydes with electron-withdrawing and electron-donating groups reacted well to give the corresponding

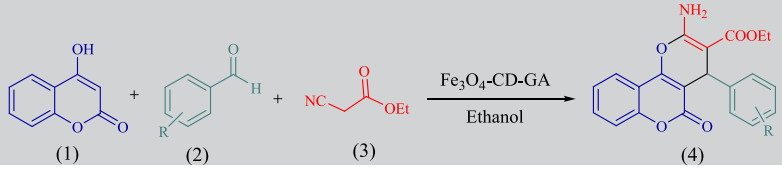
TABLE 3 Effect of solvent and temperature on the synthesis of dihydropyrano[3,2-*c*]chromenes[a]



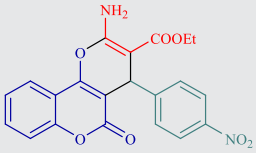
Entry	Solvent	Conditions	Time (min)	Yield (%)[b]
1	CH_2Cl_2	Reflux	180	33
2	CH_3CN	Reflux	120	47
3	H_2O	r.t.	300	35
4	H_2O	Reflux	120	50
5	EtOH	r.t.	180	65
6	EtOH	Reflux	80	89

[a]General reaction conditions: 2-chlorobenzaldehyde (1 mmol), 4-hydroxycoumarin (1 mmol) and ethyl cyanoacetate (1.1 mmol) and 0.05 g of Fe_3O_4-β-CD-GA in 5 ml of solvent.
[b]Isolated yields.
[a]*Note.* r.t., room temperature.

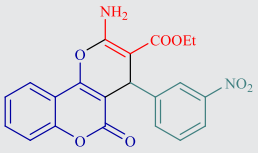
TABLE 4 Preparation of dihydropyrano[3,2-*c*]chromenes under the optimized conditions[a]



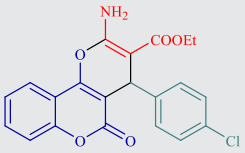
4a–4n, time (min), yield (%)[b], TON



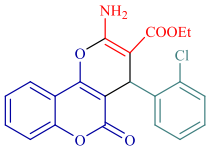
4a: 75, 90%, 56.2



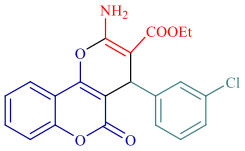
4b: 100, 83%, 51.8



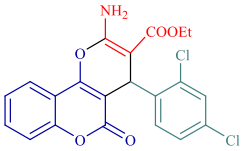
4b: 100, 83%, 51.8



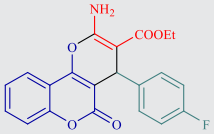
4d: 80, 89%, 55.6



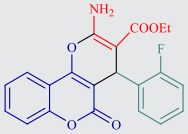
4e: 90, 87%, 54.3



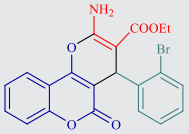
4f: 85, 88%, 55



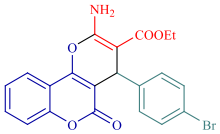
4 g: 80, 89%, 55.6



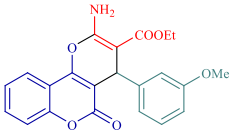
4 h: 90, 86%, 53.7



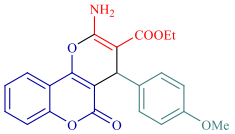
4i: 95, 83%, 51.8



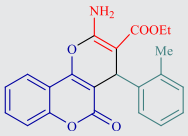
4j: 85, 85%, 53.1



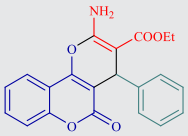
4 k: 140, 78%, 48.7



4 l: 120, 76%, 47.5



4 m: 110, 80%, 50.0



4n: 90, 85%, 53.1

Abbreviation: TON, Turn-Over Number.

[a]General reaction conditions: aldehyde (1 mmol), 4-hydroxycoumarin (1 mmol), ethyl cyanoacetate (1.1 mmol), and 0.05 g of Fe_3O_4–βCD-GA in 5 ml of ethanol.

[b]Isolated yield.

products in high yields and short reaction times. These results demonstrate that this method is an efficient approach for one-pot multicomponent synthesis of dihydropyrano[3,2-*c*]chromene derivatives. As mentioned, the synergism between the components of Fe_3O_4-β-CD-GA enhances the catalytic efficiency. We conclude that the encapsulation of the substrates within the cavity of β-CD and activation of substrates, the high basicity of GA, and the close proximity between substrates and active sites of GA facilitated the reaction. The super-paramagnetic nature of the Fe_3O_4-β-CD-GA nanocatalyst leads to simple recovery of the catalyst

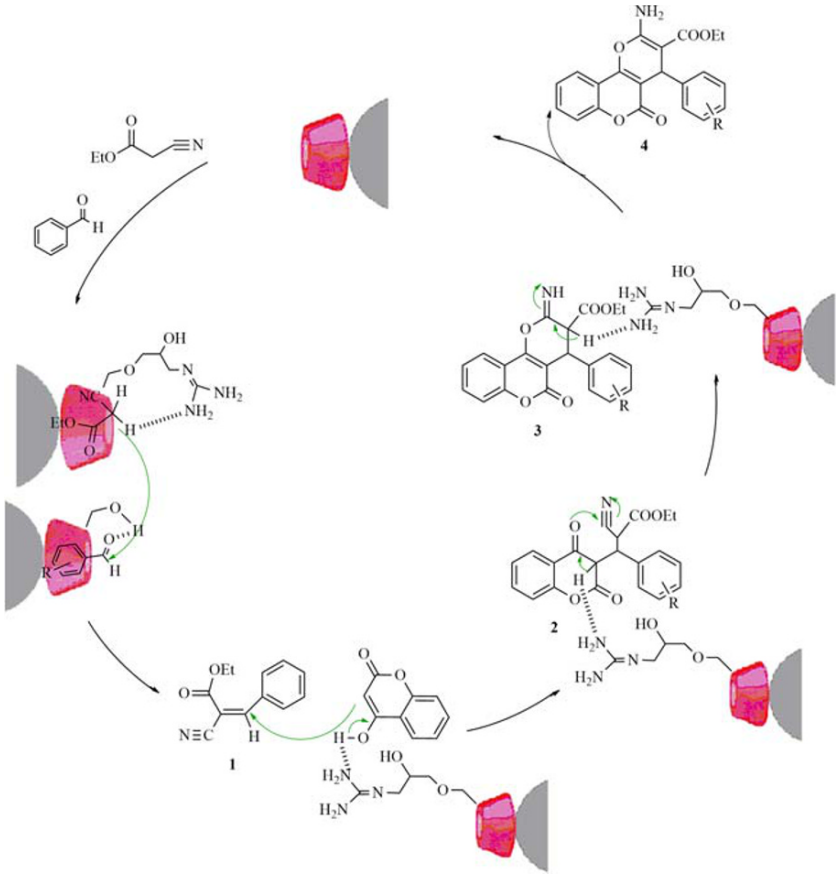
TABLE 5 Recyclability studies of the catalyst system[a]

Entry	Number of cycles	Yield (%)[b]
1	First	89
2	Cycle 1	87
3	Cycle 2	85
4	Cycle 3	83
5	Cycle 4	80

[a]General reaction conditions: mixture of 2-chlorobenzaldehyde (1 mmol), 4-hydroxycoumarin (1 mmol), and ethyl cyanoacetate (1.1 mmol) using 0.05 g of catalyst in 5 ml of EtOH was refluxed for 80 min.

[b]Isolated yields.

SCHEME 4 Proposed reaction pathway for the synthesis of dihydropyrano[3,2-*c*]chromenes using Fe_3O_4-β-CD-GA as catalyst



using an external magnet. The reactions were clean and did not require chromatographic purification. The products were isolated by a simple work-up and obtained in high purity. The structure of products was characterized by spectroscopic data such as FT-IR, ^{1}H NMR, and melting point, and the results were consistent with those of authentic samples.[47–49]

To investigate the reusability of the catalyst, after completion of the model reaction, Fe_3O_4-β-CD-GA was easily separated from reaction media by an external magnetic field. The separated catalyst was washed with ethanol and acetone several times, dried at 50°C for 10 hr and reused for the next cycle. It was found that the catalyst could be reused at least for five runs without a remarkable decrease in its catalytic performance (Table 5). Also, the inductively coupled plasma analysis of the reaction mixture after separation of the catalyst did not reveal any detectable leaching of Fe.

A probable mechanism for the synthesis of dihydropyrano[3,2-*c*]chromenes in the presence of Fe_3O_4-β-CD-GA nanocatalyst is proposed in Scheme 4. Knoevenagel condensation of activated ethyl cyanoacetate and aldehyde followed by Michel addition of 4-hydroxycoumarin with the Knoevenagel product **1** gives intermediate **2**. Then cyclization of intermediate **2** in the presence of the catalyst produces intermediate **3**, which through tautomerization forms the final product **4**. In this reaction, guanidine acts as an organic base and β-CD forms a host–guest complex through hydrogen bonding with the reactants, thereby activating them.

4 | CONCLUSION

In summary, we developed an environmentally friendly, safe, easily accessible, highly efficient, inexpensive, magnetically separable, and recyclable Fe_3O_4-β-CD-GA catalyst for one-pot three-component coupling of aromatic aldehyde, 4-hydroxycoumarin, and ethyl cyanoacetate. The reaction was efficiently performed under mild and clean conditions, giving the corresponding products in good to high isolated yields. This protocol also offers some advantages, such as short reaction times, low catalyst requirement and very easy work-up.

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